Improved Ophthalmic and Contact Lens Wetting Solutions

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Background

The present invention relates to novel ophthalmic solutions that contain a ethoxylated glyceride as an additive to improve the wettability and to decrease the degree of protein and polymeric preservative binding to contact lens surfaces. These compositions may also comprise other agents in contact lens and ophthalmic solutions such as buffers, tonicity agents, wetting agents, enzymes, hydrogen peroxide, demulcents, thickeners, sequestering agents (chelating agents), surface active agents and preservative agents. The ethoxylated glycerides are particularly useful in contact lens treatment solutions, contact lens wetting solutions, solutions used to store contact lenses and solutions used to clean or rinse contact lenses. It has been found that surprisingly the addition of ethoxylated glycerides improve the comfort of lenses treated with such solution and that this increased comfort is surprisingly long-lasting in its effect. The ethoxylated glycerides may be mono-, di- or triglycerides and include

The solutions of the present invention are made by one of two methods. First the ethoxylated glyceride may be melted and added to an aqueous solution which includes the other agents to be used in the desired formulation, or the additional agents may be added prior to the addition of the melted ethoxylated glyceride. Second, the ethoxylated glyceride may be dissolved in an alcohol base and this liquid mixture, added to the aqueous base. Ethoxylated glycerides are commercially available from numerous commercial sourcesand include Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), polyoxyl 60 hydrogenated castor oil (Cremophor RH 60), PEG-30 Castor Oil (Incrocas 30), PEG-35 Castor Oil (Cremophor EL, Incrocas 35), or PEG-40 Castor Oil (Cremophor EL, Incrocas), Cremophor EL ®, Emulphor EL ®, glycerol polyethyleneglycol riciinoleate, gycerol polyethyleneglycol oxystearate, polyethoxylated hydrogenated castor oil, or polyethoxylated vegetable oil. The ethoxylated glycerides useful in the present invention may include surfactants sold as PEG-6 Caprylic/Capric Glycerides PEG-8 Caprylic/Capric Glycerides; PEG-2 Castor Oil; PEG-3 Castor Oil; PEG-4 Castor Oil; PEG-5 Castor Oil; PEG-8 Castor Oil; PEG-9 Castor Oil; PEG-10 Castor Oil; PEG-11 Castor Oil; PEG-15 Castor Oil; PEG-20 Castor Oil; PEG-25 Castor Oil; PEG-30 Castor Oil; PEG-33 Castor Oil; PEG-35 Castor Oil; PEG-36 Castor Oil; PEG-40 Castor Oil; PEG-50 Castor Oil; PEG-54 Castor Oil; PEG-55 Castor Oil; PEG-60 Castor Oil; PEG-100 Castor Oil; PEG-200 Castor Oil; PEG-18 Castor Oil Dioleate; PEG-60 Corn Glycerides; PEG-20 Evening Primrose Glycerides;

PEG-60 Evening Primrose Glycerides; PEG-7 Glyceryl Cocoate; PEG-30 Glyceryl Cocoate; PEG-78 Glyceryl Cocoate; PEG-80 Glyceryl Cocoate; PEG-12 Glyceryl Dioleate; PEG-15 Glyceryl Isostearate; PEG-20 Glyceryl Isostearate; PEG-30 Glyceryl Isostearate; PEG-60 Glyceryl Isostearate; PEG-12 Glyceryl Laurate; PEG-20 Glyceryl Laurate; PEG-23 Glyceryl Laurate; PEG-30 Glyceryl Laurate; PEG-10 Glyceryl Oleate; PEG-15 Glyceryl Oleate; PEG-30 Glyceryl Oleate; PEG-20 Glyceryl Ricinoleate; PEG-5 Glyceryl Sesquioleate; PEG-5 Glyceryl Stearate; PEG-10 Glyceryl Stearate; PEG-25 Glyceryl Stearate; PEG-30 Glyceryl Stearate; PEG-120 Glyceryl Stearate; PEG-200 Glyceryl Stearate; PEG-28 Glyceryl Tallowate; PEG-80 Glyceryl Tallowate; PEG-200 Glyceryl Tallowate; PEG-5 Glyceryl Triisostearate; PEG-5 Hydrogenated Castor Oil; PEG-7 Hydrogenated Castor Oil; PEG-16 Hydrogenated Castor Oil; PEG-20 Hydrogenated Castor Oil; PEG-25 Hydrogenate Castor Oil; PEG-30 Hydrogenate Castor Oil; PEG-35 Hydrogenate Castor Oil; PEG-40 Hydrogenate Castor Oil; PEG-45 Hydrogenate Castor Oil; PEG-50 Hydrogenate Castor Oil; PEG-54 Hydrogenate Castor Oil; PEG-55 Hydrogenate Castor Oil; PEG-60 Hydrogenate Castor Oil; PEG-80 Hydrogenate Castor Oil; PEG-100 Hydrogenate Castor Oil; PEG-200 Hydrogenate Castor Oil; PEG-40 Hydrogenated Castor Oil PCA Isosterate; PEG-5 Hydrogenated Corn Glycerides; and PEG-8 Hydrogenated Fish Glycerides; which are all available from known commercial sources

The solutions of the present invention may contain other additives including but not limited to buffers, tonicity agents, demulcents, wetting agents, preservatives, sequestering agents (chelating agents), surface active agents, and enzymes.

Other aspects of the claimed solutions include adding to the solution from 0.001 to 1 weight percent chelating agent (preferably disodium EDTA) and/or additional microbicide, (preferably 0.00001 to 0.1 or 0.0000 1 to 0.01) weight percent polyhexamethylene biquanide (PHMB0, N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium- 1, hexetidine, bronopol, alexidine, low concentrations of hydrogen peroxide, and ophthalmologically acceptable salts thereof

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or water-soluble salts thereof, including ethylenediaminetetraacetic acid, nitrilotriacetic acid, diethylenetriamine pentaacetic acid,

hydroxyethylethylenediaminetriacetic acid, 1,2-diaminocyclohexanetetraacetic acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' tetraacetic acid (EGTA), aminodiacetic acid and hydroxyethylamino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tri- and tetra-sodium salts of ethylenediaminetetraacetic acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include citric acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphates, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and potassium salts as well as the ammonium salt.

The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.0 to 7.6. Significant deviations from neutral (pH 7.3) will cause changes in the physical parameters (i.e. diameter) in some contact lenses. Low pH (pH less than *5.5)* can cause burning and stinging of the eyes, while very low or very high pH (less than 3.0 or greater than 10) can cause ocular damage.

The additional preservatives employed in the present invention are known, such as polyhexamethylene biguanide, N-alkyl-2-pyrrolidone, chlorhexidine, polyhexamethylenebiguanide, alexidine, polyquaternium- 1, hexetidine, bronopol and a very low concentration of hydrogen peroxide, e.g., 30 to 200 ppm.

The solutions of the invention are compatible with both rigid gas permeable and hydrophilic contact lenses during storage, cleaning, wetting, soaking, rinsing and disinfection.

A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and viscosity inducing agents, which may aid in either the

lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include sodium chloride, potassium chloride, glycerol or mixtures thereof The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.5 weight percent sodium chloride.

Suitable viscosity inducing agents can include lecithin or the cellulose derivatives such as hydroxymethylcellulose, hydroxypropylcellulose and methylcellulose in amounts similar to those for surfactants, above.

EXAMPLE 1

Hydrophilic contact lenses were placed flat onto glass slides and rinsed with water to remove any debris. These slides were placed in a petri dish and covered with a few drops of each of the test solutions previously prepared in either water, an aqueous isotonic sodium chloride solution, or an aqueous phosphate buffered solution made isotonic with sodium chloride and adjusted to pH 7.3. Each *petri* plate was covered and placed in a refrigerator overnight. The following day, the slides were removed and allowed to equilibrate to room temperature. The lenses were rinsed with water and the excess water was removed. One 5 uL drop of mineral oil stained with Oil Red O was placed onto one lens for each solution. After ten minutes, the lenses were observed for the ability of the oil drop to spread.

Additive	**Solution Matrix**	**Oil Dispersibility**	**Water Dispersibility**
1% polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	water	4	5
1% polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	buffer water	5	5
1% polyoxyl 40	sodium chloride	2	5

hydrogenated castor oil (Cremophor RH 40)	water		
1% polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	buffer sodium chloride water	3	5
1% Polysorbate 80 (Tween 80)	sodium choride water	4	5
1% Poloxamine 1107 (Tetronic 1107)	sodium choride water	2	5
1% Poloxamer 407 (Pluronic F127)	sodium choride water	2	5
1% Polysorbate 80 (Tween 80)	buffer sodium chloride water	3	5
1% Poloxamine 1107 (Tetronic 1107)	buffer sodium chloride water	1	5
1% Poloxamer 407 (Pluronic F127)	buffer sodium chloride water	1	5
Water	water	1	5

Key 1 non-spreading drop
2 poor spreading drop
3 moderate spreading drop
4 increased spreading drop
5 thin spreading film

The results demonstrates that exposure of the contact lens to the ethoxylated glyceride will generate a durable modified surface capable of allow the formation of a thin oil and aqueous film. This characteristic mimics mucin and is essential for the proper tear layer formation of

over the lens. A score of 3 or better is considered acceptable. This experiment also illustrates the synergistic improvement when the ethoxylated glyceride is exposed in the presence of a buffer. The inability of the Poloxamer and Poloxamine to allow the oil film to spread across the lens demonstrates that not all surface active agents will promote the spreading of a properly formed tear film over the contact lens surface.

EXAMPLE 2

Example of Protein Deposition Inhibition

Contact lenses were soaked and heated in test solutions to which a radio-labeled lysozyme was present in a known amount for a period of 12 hours at 37 degrees Celsius. The lenses were rinsed with distilled water in order to remove residual solution. The lenses were then assayed for protein deposition using a Beckman BioGamma 1 counter. Results were reported in ug/lens.

	Lens A ug/lens	Lens B ug/lens	Average ug/lens
Phosphate buffer control	1,043	865	954
Cremophor RH40 (1%) In Phosphate Buffer	15	23	19

Ethoxylated Castor Oil was a 1 percent w/v solution. The matrix control was phosphate buffer and sodium chloride. The polyoxyl 40 hydrogenated castor oil solution had lower protein binding than the control.

EXAMPLE 3

Example of Protein Deposition Inhibition

Isotonic aqueous phosphate buffered solutions were prepared and adjusted to pH 7.4. Contact lenses were soaked in 25 mL of the test solutions overnight. Afterwards, lysozyme was added to the tubes and warmed to 37 degrees Celsius for 12 hours. The lenses were rinsed with distilled water in order to remove residual solution. The lenses were assayed for protein deposition by the BCA method and detected on an HP PDA Spectrophotometer. Results were reported in ug/lens.

Solution	ug lysozyme per lens
Marketed Product Control (phosphate buffer, Poloxamer)	>18.3
Phosphate buffer control	>26.16
Cremophor RH40 (1%) In Phosphate Buffer	9.78

Ethoxylated Castor Oil was a 1 percent w/v solution. The matrix control was phosphate buffer and sodium chloride. The polyoxyl 40 hydrogenated castor oil solution had lower protein binding than the control.

EXAMPLE 4

An example of a preferred disinfecting formulation of the subject invention is provided below in Table I. This solution is prepared by weighing out the necessary amount of the tricine, creatine, choline chloride, sodium chloride and edetate disodium into a vessel containing approximately 90% of the water volume. After each of the ingredients has dissolved, the pH is adjusted to 7.3 with either 1 N sodium hydroxide or 1 N hydrochloric acid. Following this, the polyhexamethylene biguanide is added and the solution is brought to final volume with purified water. The final product has the composition shown in the Table below.

Constituent		Weight / Volume
Polyhexamethylenebiguanide HCl	20% w/w solution available under the mark Cosmocil CQ, from Avecia	0.0001%
Tricine	Spectrum	1.0%
Creatine	Spectrum	0.25%
Choline Chloride	Amersco	0.5%
Edetate Disodium	Spectrum	0.055%
Polyoxyl 40 Hydrogenated Castor Oil	Cremophor RH 40 from BASF Co.	0.1%
Sodium Chloride	Fisher Scientific	As required for

		tonicity adjustment 300 mOsm
Hydrochloride Acid, 1N	VWR	as required for pH adjustment to 7.3
Sodium Hydroxide, 1N	Mallinckrodt	as required for pH adjustment to 7.3
Purified Water		Balance to 100%

This solution may be used to rinse, clean, and store contact lenses on a daily basis.

EXAMPLE 5

An example of a preferred formulation for a contact lens vial storage of the subject invention is provided below in Table I. This solution is prepared by weighing out the necessary amount of the sodium borate, boric acid, and sodium chloride into a vessel containing approximately 90% of the water volume. After each of the ingredients has dissolved, the pH is adjusted to 7.3 with either 1 N sodium hydroxide or 1 N hydrochloric acid. The final product had the composition shown in Table I below.

Constituent		**Weight / Volume**
Sodium Borate	Spectrum	1.0%
Boric Acid	Spectrum	0.25%
Polyoxyl 40 Hydrogenated Castor Oil	Cremophor RH40 from BASF Co.	0.1%
Sodium Chloride	Fisher Scientific	As required for tonicity adjustment 300 mOsm
Hydrochloride Acid, 1N	VWR	as required for pH adjustment to 7.3
Sodium Hydroxide, 1N	Mallinckrodt	as required for pH adjustment to 7.3
Purified Water		Balance to 100%

Example 6

The following are useful disinfecting solutions within the scope of the present invention that may be used for all purpose disinfecting solutions. They are made according to generally acceptable procedures except that the ethoxylated glycerides must be first be dissolved in warm water prior to the addition of the other components.

Constituent	Supplier	% Weight/ Volume	Amount
Purified water		to 80%	40 mL
Tricine	Spectrum	1.0%	0.500 g
Carnitine	Spectrum	0.25%	0.125 g
Betaine HCl	Spectrum	0.1%	0.050 g
Choline Chloride	Amresco	0.5%	0.250 g
Inositol	Spectrum	0.1%	0.050 g
Edetate Disodium	Spectrum	0.055%	0.0275 g
Polyoxyl 40 Hydrogenated Castor Oil	Cremophor RH 40 from BASF Co.	0.1%	0.5 mL of 10%
Hydrochloride Acid, 1N		as required for pH adjustment to 7.3	as required for pH adjustment to 7.3
Sodium Hydroxide, 1N		as required for pH adjustment to 7.3	as required for pH adjustment to 7.3
Purified Water		to 98%	Dilute to 49 mL
Sodium Chloride	Fisher	As required for tonicity adjustment 300 mOsm	As required for tonicity adjustment 300 mOsm
Polyhexamethylene-biguanide HCl	20% w/w solution available under the mark Cosmocil CQ from Avecia	0.0001%	50 uL of 0.1%
Purified Water		Balance to 100%	Dilute to 50 mL

Example 7

The following are formulations within the scope of the invention of formulations intended to be used as lens-vial solutions that are used to store lenses prior to their use. These solutions have the effect of treating the contact lens in the solution and rendering the lens more comfortable in use.

Constituent	Supplier	% Weight/ Volume	Amount
Purified water		to 80%	40 mL
Tricine	Spectrum	1.0%	0.500 g
Carnitine	Spectrum	0.25%	0.125 g
Inositol	Spectrum	0.1%	0.050 g
Hydrochloride Acid, 1N		as required for pH adjustment to 7.3	as required for pH adjustment to 7.3
Sodium Hydroxide, 1N		as required for pH adjustment to 7.3	as required for pH adjustment to 7.3
Polyoxyl 40 Hydrogenated Castor Oil	Cremophor RH 40 from BASF Co.	0.1%	0.5 mL of 10%
Purified Water		to 98%	Dilute to 49 mL
Sodium Chloride	Fisher	As required for tonicity adjustment 300 mOsm	As required for tonicity adjustment 300 mOsm
Purified Water		to 100%	Dilute to 50 mL